



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 870

[Docket No. FDA-2013-N-0487]

Cardiovascular Devices; Reclassification of External Counter-Pulsating Devices for Treatment of Chronic Stable Angina; Effective Date of Requirement for Premarket Approval for External Counter-Pulsating Devices for Other Specified Intended Uses

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed administrative order to reclassify external counter-pulsating (ECP) devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization, which is a preamendments class III device, into class II (special controls) based on new information. FDA is also proposing to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for ECP devices for other intended uses specified in this proposed order. The Agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the devices to meet the statute's approval requirements for other intended uses specified in this proposed order. In addition, FDA is announcing the opportunity for interested persons to request that the Agency change the classification of any of the devices mentioned in this document based on new information. This action implements certain statutory requirements.

DATES: Submit either electronic or written comments on this proposed order by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. FDA intends that, if a final order based on this proposed order is issued, anyone who wishes to continue to market ECP devices for specified intended uses listed in section IX will need to file a PMA or a notice of completion of a PDP within 90 days of the effective date of the final order. See section XVII for the proposed effective date of any final order based on this proposed order.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-0487, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-0487 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the SUPPLEMENTARY INFORMATION section.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Angela Krueger, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 1666, Silver Spring, MD 20993, 301-796-6380, angela.krueger@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (Public Law 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), the Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250), the Medical Devices Technical Corrections Act (Public Law 108-214), the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments

devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type may be marketed without submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval or until the device is subsequently reclassified into class I or class II.

Although, under the FD&C Act, the manufacturer of class III preamendments device may respond to the call for PMAs by filing a PMA or a notice of completion of a PDP, in practice, the option of filing a notice of completion of a PDP has not been used. For simplicity, although

corresponding requirements for PDPs remain available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing and receiving approval of a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act, changing the process for reclassifying a device from rulemaking to an administrative order. Section 608(b) of FDASIA (126 Stat. 1056) amended section 515(b) of the FD&C Act, changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

A. Reclassification

FDA is publishing this document to propose the reclassification of ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization from class III to class II.

Section 513(e) of the FD&C Act governs reclassification of classified preamendments devices. This section provides that FDA may, by administrative order, reclassify a device based upon "new information." FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term "new information," as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland-Rantos Co. v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent action where the reevaluation is made in light of newly available authority (see Bell, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F.Supp. 382, 388-391 (D.D.C. 1991)), or in light of changes in "medical science" (Upjohn, 422 F.2d at 951). Whether data before the Agency are old or new data, the "new information" to support reclassification under section 513(e) must be "valid scientific evidence," as defined in section 513(a)(3) of the FD&C Act and § 860.7(c)(2) (21 CFR 860.7(c)(2)). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Association v. FDA, 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985).)

FDA relies upon "valid scientific evidence" in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).) Section 520(h)(4) of the FD&C Act, added by FDAMA, provides that FDA may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This can include information from clinical and preclinical tests or studies that demonstrate the safety or effectiveness of the device but does not include descriptions of methods of manufacture or product composition and other trade secrets.

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to a public docket. FDA has held a meeting of a device classification panel described

in section 513(b) of the FD&C Act with respect to external-counter pulsating devices, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act.

FDAMA added section 510(m) to the FD&C Act. Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act, if the Agency determines that premarket notification is not necessary to assure the safety and effectiveness of the device.

B. Requirement for Premarket Approval Application

FDA is proposing to require PMAs for ECP devices for Certain Specified Intended Uses.¹

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers. FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to external-counter pulsating devices, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act.

¹ For the purposes of this proposed order, the term "Certain Specified Intended Uses" includes the following intended uses:

- Unstable angina pectoris;
- Acute myocardial infarction;
- Cardiogenic shock;
- Congestive heart failure;
- Postoperative treatment of patients who have undergone coronary artery bypass surgery;
- Peripheral arterial disease associated with the following: Ischemic ulcers rest pain or claudication; threatened gangrene; insufficient blood supply at an amputation site; persisting ischemia after embolectomy or bypass surgery; and/or pre- and post-arterial reconstruction to improve runoff;
- Diabetes complicated by peripheral arterial disease or other conditions possibly related to arterial insufficiency including the following: Nocturnal leg cramps and/or necrobiosis diabetorum;
- Venous diseases, including the following: Prophylaxis of deep vein thrombophlebitis; edema (e.g., chronic lymphedema) and/or induration (e.g., stasis dermatitis) associated with chronic venous stasis; venous stasis ulcers; and/or thrombophlebitis;
- Athletic injuries, including the following: Charley horses, pulled muscles, and/or edematous muscles; and
- Necrotizing cellulitis.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or a declared completed PDP and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order and the proposed findings, and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f)

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA is considered to be a final order for purposes of section 501(f) of the FD&C Act (21 U.S.C. 351(f))) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. For ECP devices, the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since these devices were classified in 1980, the 30-month period has expired (45 FR 7966; February 5, 1980). Therefore, if the proposal to

require premarket approval for ECP devices for Certain Specified Intended Uses is finalized, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such device be filed within 90 days of the date of issuance of the final order. If a PMA is not filed for such device within 90 days after the issuance of a final order, the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Other enforcement actions include, but are not limited to, the following: Shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). In the past, FDA has requested that manufacturers take action to prevent the further use of devices for which no PMA has been filed and may determine that such a request is appropriate for the class III devices that are the subject of this proposed order, if finalized.

In accordance with section 515(b)(2) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of ECP devices for Certain Specified Intended Uses.

II. Regulatory History of the Device

In the preamble to the proposed rule (44 FR 13426, March 9, 1979), the Cardiovascular Device Classification Panel (the 1979 Panel) recommended that ECP devices be classified into class III because the device is life-supporting and is potentially hazardous to life or health even when properly used. The 1979 Panel noted that the device surrounds the limbs to which it is attached, is in direct contact with the skin, and is used in a clinical environment where excessive leakage current can be a serious hazard. As a result the electrical characteristics of this device need to meet certain requirements. The 1979 Panel further noted that the performance characteristics, including accuracy, reproducibility, and any limitations on the device's cardiac synchronization and pressure application should be maintained at a generally accepted satisfactory level and should be made known to the user through special labeling. In addition, the device is used with other devices in a system that may be hazardous if not satisfactorily assembled, used, and maintained. The 1979 Panel indicated that general controls alone would not provide sufficient control over the performance characteristics of the device, and that there was not sufficient information to establish a performance standard to provide assurance of the safety and effectiveness of the device. Consequently, the 1979 Panel believed that premarket approval was necessary to assure the safety and effectiveness of the device. In 1980, FDA classified external counter-pulsating devices into class III after receiving no comments on the proposed rule (45 FR 7966, February 5, 1980).

In 1987, FDA published a clarification by codifying a statement that no effective date had been established for the requirement for premarket approval for external counter-pulsating devices (52 FR 17732 at 17737, May 11, 1987).

In 2009, FDA published an order for the submission of information on external counter-pulsating devices by August 7, 2009 (74 FR 16214, April 9, 2009). FDA received five responses to that order from device manufacturers recommending that ECP devices be reclassified to class II. The manufacturers stated that safety and effectiveness of these devices may be assured by device design, performance testing, and labeling (special controls).

As explained further in sections VII and XI, a meeting of the Circulatory System Devices Panel (the 2012 Panel) took place December 5, 2012, to discuss whether ECP devices should be reclassified or remain in class III. The 2012 Panel recommended that ECP devices intended for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization be reclassified to class II with special controls and ECP devices for Certain Specified Intended Uses remain in class III. Because the safety and effectiveness of ECP devices for Certain Specified Intended Uses has not been established through adequate scientific evidence, the device presents a potential unreasonable risk of injury given that the benefit of ECP devices for these uses is unknown. In addition, there was insufficient information to establish special controls for these uses. FDA is not aware of new information that would provide a basis for a different recommendation or findings.

III. Device Description

An external counter-pulsating device is a noninvasive device used to assist the heart by applying positive or negative pressure to one or more of the body's limbs in synchrony with the heart cycle. An ECP system typically consists of a treatment table, a set of pressure cuffs, and a

control console. The control console controls a pneumatic circuit that inflates and deflates the pressure cuffs. The inflatable pressure cuffs are wrapped around the calves, the lower and upper thighs, and/or the buttocks. They are rapidly and sequentially inflated, starting from the calves and moving proximally during the diastolic phase of a cardiac cycle. This creates an arterial retrograde flow of blood towards the heart and increases blood flow to the coronary arteries at a time when resistance to the coronary blood flow is low. The inflation of the cuffs also simultaneously increases the volume of venous blood returned to the right side of the heart, providing greater filling of the ventricle for ejection. The synchronization between the cardiac cycle and the inflation/deflation cycle of the cuffs is coordinated by custom software contained within the control console that monitors and interprets the patient's electrocardiogram and heart rhythm.

IV. Proposed Reclassification

FDA is proposing that ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization be reclassified from class III to class II. In this proposed order, the Agency has identified special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls applicable to the devices, would provide reasonable assurance of their safety and effectiveness. Absent the special controls identified in this proposed order, general controls applicable to the device are insufficient to provide reasonable assurance of the safety and effectiveness of the device.

Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and § 860.130, based on new information with respect to the devices and taking into account the public health benefit of the use of the device and the nature and known incidence of the risk of

the device, FDA, on its own initiative, is proposing to reclassify this preamendments class III device into class II for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. FDA believes that this new information is sufficient to demonstrate that the proposed special controls can effectively mitigate the risks to health identified in the next section, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness for ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization.

Section 510(m) of the FD&C Act authorizes the Agency to exempt class II devices from premarket notification (510(k)) submission. FDA has considered ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization in accordance with the reserved criteria set forth in section 513(a) of the FD&C Act and decided that the device does require premarket notification. Therefore, the Agency does not intend to exempt this proposed class II device from premarket notification (510(k)) submission.

V. Risks to Health

After considering available information, including the recommendations of the advisory committees (panels) for the classification of these devices, FDA has evaluated the risks to health associated with the use of ECP devices and determined that the following risks to health are associated with its use:

- Cardiac arrhythmias--Excessive electrical leakage current may disturb the normal electrophysiology of the heart, leading to the onset of cardiac arrhythmias.

- Trauma/Irritation to the limb--Improper mechanical design, including selection of materials, may cause bruising, blistering, muscle aches, and/or pain to the limb(s).
- Ineffective cardiac assistance--Improper timing or failure to synchronize the device with the appropriate phase of the cardiac cycle may lead to ineffective cardiac assistance by the device.

VI. Summary of Reasons for Reclassification

If properly manufactured and used, ECP devices can provide a treatment option for patients with chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization, especially patients who are not candidates for treatment by revascularization and who are refractory to medical therapy, by increasing blood flow to the coronary arteries and increasing the volume of venous blood returned to the right side of the heart, providing greater filling of the ventricle for ejection. FDA believes that ECP devices intended for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization should be reclassified from class III to class II because special controls, in addition to general controls, can be established to provide reasonable assurance of the safety and effectiveness of the device, and because general controls themselves are insufficient to provide reasonable assurance of its safety and effectiveness. In addition, there is now adequate effectiveness information sufficient to establish special controls to provide such assurance.

VII. Summary of Data Upon Which the Reclassification Is Based

Since the time of the 1979 Panel recommendation, sufficient evidence has been developed to support a reclassification of ECP devices to class II with special controls for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and

without options for revascularization. FDA has been reviewing these devices for many years and their risks are well known. FDA conducted a comprehensive review of available literature for ECP devices for treatment of chronic stable angina. FDA's review found 4 randomized controlled trials (Refs. 1 to 4), 21 observational studies, and a meta-analysis of 13 individual studies that provided consistent evidence of the effectiveness of ECP devices for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. Although all of the studies of ECP for the treatment of angina considered individually have various limitations, the consistency of the study results, the wide range of angina-related endpoints involved in the studies, the large magnitude of the demonstrated beneficial outcomes, the long duration (up to 3 years) of some of the beneficial outcomes, and the fact that many or most of the subjects had a disease that was refractory to the effects of any other treatment, all support a conclusion of reasonable evidence for the effectiveness of ECP in the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. The safety profile of ECP devices has been established based on the few relevant adverse events reported in the literature or through FDA's Manufacturer and User Facility Device Experience (MAUDE) database. In addition, bench studies designed to demonstrate the devices' ability to function as intended have been well characterized.

The 2012 Panel discussed and made recommendations regarding the regulatory classification of ECP devices to either reconfirm to class III (subject to premarket approval application) or reclassify to class II (subject to special controls) as directed by section 515(i) of the FD&C Act.

FDA's presentation to the 2012 Panel included a summary of the available safety and effectiveness information for ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization, including adverse event reports from the MAUDE database and available literature. Based on the available scientific literature that supports that ECP may be beneficial for patients with chronic stable angina who are not revascularization candidates and who are refractory to optimal medical therapy, FDA recommended to the 2012 Panel that ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization be reclassified to class II (special controls). The 2012 Panel agreed with FDA's conclusion that the available scientific evidence is adequate to support the safety and effectiveness of ECP devices for treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization.

The 2012 Panel also agreed with the identified risks to health outlined in section V. FDA recommended that a fourth risk to health, failure to identify the correct patient population, be considered in the 2012 Panel's deliberations. FDA proposed this risk to health to capture situations in which the device was used properly but patients experienced adverse events associated with their underlying comorbidities. For example, based on FDA's evaluation of Medical Device Reporting Regulations more than half were associated with patients with congestive heart failure who experience exacerbation of the condition following use of the device. However, the 2012 Panel questioned whether failure to identify the correct patient population was really a risk to health and noted that the risk is vague and too broad. FDA agreed with the 2012 Panel's recommendation and removed the proposed fourth risk. The 2012 Panel agreed with FDA's proposed special controls outlined in section VIII. In addition, the 2012

Panel also agreed with FDA that ECP devices are not considered to be life-supporting. This differs from the 1979 Panel's recommendation outlined in the proposed rule for this device type (44 FR 13426, March 9, 1979). The 2012 Panel transcript and other meeting materials are available on FDA's Web site (Ref. 5).

VIII. Proposed Special Controls

FDA believes that the following special controls, together with general controls, are sufficient to mitigate the risks to health described in section V:

- (1) Nonclinical performance evaluation of the device must demonstrate a reasonable assurance of safety and effectiveness for applied pressure, synchronization of therapy with the appropriate phase of the cardiac cycle, and functionality of alarms during a device malfunction or an abnormal patient condition;
- (2) Reliabilities of the mechanical and electrical systems must be established through bench testing under simulated use conditions and matched by appropriate maintenance schedules;
- (3) Software design and verification and validation must be appropriately documented;
- (4) The skin-contacting components of the device must be demonstrated to be biocompatible;
- (5) Appropriate analysis and testing must be conducted to verify electrical safety and electromagnetic compatibility of the device; and
- (6) Labeling must bear all information required for the safe and effective use of the device, including a detailed summary of the device-related and procedure-related complications pertinent to use of the device.

ECP devices are prescription devices restricted to patient use only upon the authorization of a practitioner licensed by law to administer or use the device. (Proposed § 870.5225(a) (21 CFR 870.5225(a)); see section 520(e) of the FD&C Act and 21 CFR 801.109 (Prescription devices)). Prescription-use requirements are a type of general control authorized under section 520(e) of the FD&C Act and defined as a general control in section 513(a)(1)(A)(i) of the FD&C Act; and under § 807.81, the device would continue to be subject to 510(k) notification requirements.

IX. Dates New Requirements Apply

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency within 90 days after issuance of any final order based on this proposal for ECP devices intended for the following uses (Certain Specified Intended Uses):

- Unstable angina pectoris;
- Acute myocardial infarction;
- Cardiogenic shock;
- Congestive heart failure;
- Postoperative treatment of patients who have undergone coronary artery bypass surgery;
- Peripheral arterial disease associated with the following: Ischemic ulcers rest pain or claudication, threatened gangrene, insufficient blood supply at an amputation site, persisting ischemia after embolectomy or bypass surgery, and/or pre and post-arterial reconstruction to improve runoff;
- Diabetes complicated by peripheral arterial disease or other conditions possibly related to arterial insufficiency including the following: Nocturnal leg cramps and/or necrobiosis diabetorum;

- Venous diseases, including the following: Prophylaxis of deep vein thrombophlebitis, edema (e.g., chronic lymphedema) and/or induration (e.g., stasis dermatitis) associated with chronic venous stasis, venous stasis ulcers, and/or thrombophlebitis;
- Athletic injuries, including the following: Charley horses, pulled muscles, and/or edematous muscles; and
- Necrotizing cellulitis.

An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, will be permitted to continue marketing such class III devices during FDA's review of the PMA provided that the PMA is timely filed. FDA intends to review any PMA for the device within 180 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that "the continued availability of the device is necessary for the public health."

An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, who does not intend to market such device for any one or more Certain Specified Intended Uses, may remove such intended uses from the device's labeling by initiating a correction within 90 days after issuance of any final order based on this proposal. 21 CFR 806.10(a)(2) requires a device manufacturer or importer initiating a correction to remedy a violation of the FD&C Act that may present a risk to health to submit a written report of the correction to FDA.

FDA intends that under § 812.2(d), the preamble to any final order based on this proposal will state that, as of the date on which the filing of a PMA is required to be filed, the exemptions from the requirements of the IDE regulations for preamendments class III devices in

§ 812.2(c)(1) and (c)(2) will cease to apply to any device that is: (1) Not legally on the market on or before that date or (2) legally on the market on or before that date but for which a PMA is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA for a class III device is not filed with FDA within 90 days after the date of issuance of any final order requiring premarket approval for the device, the device would be deemed adulterated under section 501(f) of the FD&C Act. The device may be distributed for investigational use only if the requirements of the IDE regulations are met. The requirements for significant risk devices include submitting an IDE application to FDA for review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, recommends that IDE applications be submitted to FDA at least 30 days before the end of the 90-day period after the issuance of the final order to avoid interrupting any ongoing investigations.

Because ECP devices intended for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization can currently be marketed after receiving clearance of an application for premarket notification, and FDA is proposing to reclassify these devices as class II requiring clearance of an application for premarket notification, this order, if finalized, will not require a new premarket submission for ECP devices intended for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization.

X. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by

requiring that this device have an approved PMA for Certain Specified Intended Uses and (2) the benefits to the public from the use of ECP devices for Certain Specified Intended Uses.

These findings are based on the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted in response to the 515(i) order (74 FR 16214, April 9, 2009) and any additional information that FDA has obtained. Additional information regarding the risks as well as classification associated with this device type can be found in 44 FR 13426, 45 FR 7966, and 52 FR 17732 at 17737.

XI. Device Subject to the Proposal to Require a PMA--External Counter-Pulsating Devices for Uses Other Than Treatment of Chronic Stable Angina That Is Refractory to Optimal Anti-anginal Medical Therapy and Without Options for Revascularization (§ 870.5225(c))

A. Identification

An external counter-pulsating device is a noninvasive, prescription device used to assist the heart by applying positive or negative pressure to one or more of the body's limbs in synchrony with the heart cycle.

B. Summary of Data

For uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization as specified in section IX, FDA concludes that the safety and effectiveness of these devices have not been established by adequate scientific evidence. There is limited scientific evidence regarding the effectiveness of ECP devices for uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. Review of the published scientific literature revealed a lack of valid scientific evidence to support indications other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and

without options for revascularization. There were few studies that discussed other uses and those studies did not provide evidence of reasonable assurance of effectiveness due to lack of relevant details regarding study design, conduct and results, use of flawed study designs, and publication bias (Refs. 6 to 11). FDA presented the findings of our literature search for ECP devices for uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization to the Circulatory System Devices Panel (the Panel) on December 5, 2012. Based on FDA's findings, the Panel concluded that available scientific evidence is not adequate to support the effectiveness of ECP devices for uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. The Panel also recommended that ECP devices for Certain Specified Intended Uses should remain in class III (subject to premarket approval application). Although the Panel noted that ECP devices are not life-supporting, the devices present a potential unreasonable risk of injury given that risks to health exist that are not balanced by a benefit that has been established through adequate scientific evidence to demonstrate safety and effectiveness.

The Panel transcript and other meeting materials are available on FDA's Web site (Ref. 5).

C. Risks to Health

The risks to health for ECP devices for uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization are the same as outlined in section V.

D. Benefits of ECP Devices

As discussed previously, there is limited scientific evidence regarding the effectiveness of ECP devices for uses other than treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. Because the benefits of these devices for such uses are unknown, it is impossible to estimate the direct effect of the devices on patient outcomes. However, claims for the devices state that the devices have the potential to benefit the public by augmenting cardiac output, increasing coronary blood flow, and stimulating circulation in the lower extremities.

XII. PMA Requirements

A PMA for ECP devices for Certain Specified Intended Uses must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see § 860.7(c)(1)). Valid scientific evidence is "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from

which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use...Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness." (See § 860.7(c)(2).)

XIII. Opportunity to Request a Change in Classification

Before requiring the filing of a PMA for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of ECP devices for Certain Specified Intended Uses is to be in the form of a reclassification petition containing the information required by § 860.123, including new information relevant to the classification of the device.

XIV. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices and section 515(b) of the FD&C Act provided for FDA to issue regulations to require approval of an application for premarket approval for preamendments devices or devices found to be substantially equivalent to preamendments devices. Because sections 513(e) and 515(b) as amended require FDA to issue final orders rather than regulations, FDA will continue to codify reclassifications and requirements for approval of an application for premarket approval, resulting from changes issued in final orders, in the Code of Federal Regulations. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended

by FDASIA, in this proposed order, we are proposing to revoke the requirements in § 870.5225 related to the classification of external counter-pulsating devices for chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization as class III devices and to codify the reclassification of external counter-pulsating devices for chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization into class II.

XV. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XVI. Paperwork Reduction Act of 1995

This proposed order refers to collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The collections of information in 21 CFR part 814 have been approved under OMB control number 0910-0231. The collections of information in part 807, subpart E, have been approved under OMB control number 0910-0120.

The effect of this order, if finalized, is to shift certain devices from the 510(k) premarket notification process to the PMA process. FDA estimates that there will be two fewer 510(k) submissions as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 91-hour burden decrease to OMB control number 0910-0120, which is the control number for the 510(k) premarket notification process. However, because FDA does not expect to receive any new PMAs as a result of this order, we estimate no burden increase to OMB control

number 0910-0231 based on this order, if finalized. Therefore, on net, FDA expects a burden hour decrease of 91 due to this proposed regulatory change.

The collections of information in part 812 have been approved under OMB control number 0910-0078.

XVII. Proposed Effective Date

FDA is proposing that any final order based on this proposed order become effective 90 days after date of publication of the final order in the Federal Register.

XVIII. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to submit one set of comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

XIX. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site address in this reference section, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

1. Arora, R. R., T. M. Chou, D. Jain, et al., "The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-

Induced Myocardial Ischemia and Anginal Episodes," Journal of the American College of Cardiology, vol. 33, pp. 1833-1840, 1999.

2. Arora, R. R., T. M. Chou, D. Jain, et al., "Effects of Enhanced External Counterpulsation on Health-Related Quality of Life Continue 12 Months After Treatment: A Substudy of the Multicenter Study of Enhanced External Counterpulsation," Journal of Investigative Medicine, vol. 50, pp. 25-32, 2002.

3. Gloekler, S., P. Meier, S. F. de Marchi, et al., "Coronary Collateral Growth by External Counterpulsation: A Randomised Controlled Trial," Heart, vol. 96, pp. 202-207, 2010.

4. Casey, D. P., D. T. Beck, W. W. Nichols, et al., "Effects of Enhanced External Counterpulsation on Arterial Stiffness and Myocardial Oxygen Demand in Patients With Chronic Angina Pectoris," American Journal of Cardiology, vol. 107, pp. 1466-1472, 2011.

5. FDA, the Panel transcript and other meeting materials, (<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm300073.htm>).

6. Abbottsmith, C. W., E. S. Chung, T. Varricchione, et al., "Enhanced External Counterpulsation Improves Exercise Duration and Peak Oxygen Consumption in Older Patients With Heart Failure: A Subgroup Analysis of the PEECH Trial," Congestive Heart Failure, vol. 12, pp. 307-311, 2006.

7. Feldman, A. M., M. A. Silver, G. S. Francis, et al., "Enhanced External Counterpulsation Improves Exercise Tolerance in Patients With Chronic Heart Failure," Journal of the American College of Cardiology, vol. 48, pp. 1198-1205, 2006.

8. Kozdag, G., G. Ertas, F. Aygun, et al., "Clinical Effects of Enhanced External Counterpulsation Treatment in Patients With Ischemic Heart Failure," Anadolu Kardiyol Derg, vol. 12, pp. 214-221, 2012.
9. Triulzi, E., S. Devizzi, G. Rovelli, et al., ["Efficacy of Enhanced Aortic Diastolic Pressure With An External Counterpulsation Method in the Acute Myocardial Infarction" (author's translation)], Giornale Italiano di Cardiologia, vol. 10, pp. 690-702, 1980.
10. Vijayaraghavan, K., L. Santora, J. Kahn, et al., "New Graduated Pressure Regimen for External Counterpulsation Reduces Mortality and Improves Outcomes in Congestive Heart Failure: A Report From the Cardiomedics External Counterpulsation Patient Registry," Congestive Heart Failure, vol. 11, pp. 147-152, 2005.
11. Amsterdam, E. Z., J. Banas, J. M. Criley, et al., "Clinical Assessment of External Pressure Circulatory Assistance in Acute Myocardial Infarction," American Journal of Cardiology, vol. 45, pp. 349-356, 1980.

List of Subjects in 21 CFR Part 870

Medical devices, Cardiovascular devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 870 be amended as follows:

PART 870--CARDIOVASCULAR DEVICES

1. The authority citation for 21 CFR part 870 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Revise § 870.5225 to read as follows:

§ 870.5225 External counter-pulsating device.

(a) Identification. An external counter-pulsating device is a noninvasive, prescription device used to assist the heart by applying positive or negative pressure to one or more of the body's limbs in synchrony with the heart cycle.

(b) Classification. (1) Class II (special controls) when the device is intended for the treatment of chronic stable angina that is refractory to optimal anti-anginal medical therapy and without options for revascularization. The special controls for this device are:

- (i) Nonclinical performance evaluation of the device must demonstrate a reasonable assurance of safety and effectiveness for applied pressure, synchronization of therapy with the appropriate phase of the cardiac cycle, and functionality of alarms during a device malfunction or an abnormal patient condition;
- (ii) Reliabilities of the mechanical and electrical systems must be established through bench testing under simulated use conditions and matched by appropriate maintenance schedules;
- (iii) Software design and verification and validation must be appropriately documented;
- (iv) The skin-contacting components of the device must be demonstrated to be biocompatible;
- (v) Appropriate analysis and testing must be conducted to verify electrical safety and electromagnetic compatibility of the device; and
- (vi) Labeling must bear all information required for the safe and effective use of the device, including a detailed summary of the device-related and procedure-

related complications pertinent to use of the device.

(2) Class III (premarket approval) for the following intended uses: Unstable angina pectoris; acute myocardial infarction; cardiogenic shock; congestive heart failure; postoperative treatment of patients who have undergone coronary artery bypass surgery; peripheral arterial disease associated with ischemic ulcers rest pain or claudication, threatened gangrene, insufficient blood supply at an amputation site, persisting ischemia after embolectomy or bypass surgery, and/or pre- and post-arterial reconstruction to improve runoff; diabetes complicated by peripheral arterial disease or other conditions possibly related to arterial insufficiency including nocturnal leg cramps and/or necrobiosis diabetorum; venous diseases, including prophylaxis of deep vein thrombophlebitis, edema (e.g., chronic lymphedema) and/or induration (e.g., stasis dermatitis) associated with chronic venous stasis, venous stasis ulcers, and/or thrombophlebitis; athletic injuries, including Charley horses, pulled muscles and/or edematous muscles; necrotizing cellulitis.

(c) Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with FDA on or before [A DATE WILL BE ADDED THAT WILL BE 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], for any external counter-pulsating device, with an intended use described in (b)(2) of this section, that was in commercial distribution before May 28, 1976, or that has, on or before [A DATE WILL BE ADDED THAT WILL BE 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], been found to be substantially equivalent to any external counter-pulsating device, with an intended use described in (b)(2) of this section, that was in commercial distribution before May 28, 1976. Any other

external counter-pulsating device with an intended use described in (b)(2) of this section shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: May 15, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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